AFT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/713,136	11/14/2000	Stephen Tuck	3778820001500	3530

25226 7590 04/21/2004

MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/713,136	TUCK ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-42,63,65-86,88,89,94-101 and 106-108* is/are pending in the application.

4a) Of the above claim(s) *11-42,65-70,73,76-82,85,88 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63,71,72,74,75,83,84,86,94-101 and 106-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11-42, 63, 65-86, 88-89, 94-101 and 106-108 are pending.

2. Claims 11-42, 65-70, 73, 76-82, 85, and 88-89 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 63, 71-72, 74-75, 83-84, 86, and 94-101, 106-108 that read on species "Amb a1" as the specific antigen and "AACGTTCG" as a specific ISS are being acted upon in this Office Action.

4. The following new grounds of rejection are necessitated by the amendment filed 11/4/03.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate to (ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is about 3.5 to about 6.0; (2) A population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides a 40% histamine release from basophiles of an allergen-sensitized individual is greater than about 500, said ratio is calculated as the ratio of (i) concentration of ISS-allergen conjugate to (ii) concentration of antigen required for 40% histamine release from basophiles from an allergen sensitized individual; (3) A population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen such as Amb a1 and a polynucleotide *consisting* of an

immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule; (4) A composition comprising the population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen and a polynucleotide *consisting* of an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule in a pharmaceutically acceptable excipient; (5) A population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence such as the ones recited in claims 79, 81, 82, 84 and 85, and wherein the extent of conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1; (6) A composition comprising the population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1 in a pharmaceutically acceptable excipient for treating allergy, **does not** reasonably provide enablement for *any* immunostimulatory sequence (ISS) such as any ISS "comprises" the sequence 5'cytosine, guranine-3' wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, *any* ISS "comprises" the sequence 5'purine, purine, C, G, pyrimidine, pyrimidine, C,G-3', *any* ISS "comprises" a sequence set forth in claim 72 in the conjugate molecule of the claimed population as set forth in claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only eight specific immunostimulatory sequences (ISS) selected from the group consisting of SEQ ID NO: 1-8 conjugated to ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, lines 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

The specification does not teach how to make any ISS "comprises" any nucleotides greater than 6 and less about 200 nucleotides in length mentioned above because the term "comprises" is open-ended. It expands the immunostimulatory sequence (ISS) to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine. There is insufficient guidance as to which undisclosed nucleotide to be added and whether the resulting undisclosed has immune stimulatory activity. Further, the specification discloses only ISS of 6, 8 and 22 nucleotides in length. The rest of the nucleotides within the ISS are not 194 nucleotides are not adequate taught in the specification.

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al* teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant for triggering autoimmune disease in predisposed susceptible individual (See abstract, in particular).

Yamada *et al* teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Given the

indefinite number of antigen conjugated to indefinite number of undisclosed ISS, there is insufficient working examples demonstrating that any conjugate molecules mentioned above is immunostimulatory, let alone useful for treating any disease.

Given the indefinite number of undisclosed ISS, polynucleotide, it is unpredictable which undisclosed polynucleotide has stimulatory activity. Since the ISS in the conjugate molecule is not enabled, it follows that claimed population of conjugate molecule and composition comprising the undisclosed ISS is not enabled.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/4/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the term antigen is defined on page 16 and 17 and many examples of antigens known in the art are provided on pages 43-50. (2) The cited reference Yamada and Segal do not appear to the enablement of the claimed populations of conjugate molecules. The amended claims are directed to conjugate populations in which the ISS containing polynucleotide is greater than 6 and less than about 200 nucleotides in length and the ISS comprises the sequence 5'-C, G-3'. (3) The Office has recently issued claims directed to methods of treating a subject through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS wherein the ISS comprises the sequence 5'-C, G-3 (See US Pat 6,613,751, 6,552,006; 6,534,062 and 6,498,148).

In response, the claims still encompass a population of conjugated molecule comprising a genus of antigen, allergen, polypeptide conjugated to and a genus of polynucleotide comprising *any* immunostimulatory sequence (ISS) wherein the ISS "comprises" a nucleotide sequence greater than 6 and less than about 200 nucleotides in length having a sequence 5'-C, G-3'.

The specification merely discloses only eight specific immunostimulatory sequences (ISS) selected from the group consisting of SEQ ID NO: 1-8 conjugated to only ragweed allergen Amb a1 (See page 72).

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al* teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant for triggering autoimmune disease in predisposed susceptible individual (See abstract, in particular).

Yamada *et al* teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Given the indefinite number of antigen conjugated to indefinite number of undisclosed ISS, there is insufficient working examples demonstrating that any conjugate molecules mentioned above is immunostimulatory, let alone useful for treating any disease.

Given the indefinite number of undisclosed ISS, polynucleotide, it is unpredictable which undisclosed polynucleotide has stimulatory activity. Since the ISS in the conjugate molecule is not enabled, it follows that claimed population of conjugate molecule and composition comprising the undisclosed ISS is not enabled.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

In response to applicant's argument that the Office has recently issued claims directed to methods of treating a subject through administering an immunostimulatory or immunomodulatory

polynucleotide comprising an ISS wherein the ISS comprises the sequence 5'-C, G-3, every application is examined on its own merits.

7. Claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* immunostimulatory sequence (ISS) such as any ISS "comprises" the sequence 5'cytosine, guranine-3' wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, *any* ISS "comprises" the sequence 5'purine, purine, C, G, pyrimidine, pyrimidine, C,G-3', *any* ISS "comprises" a sequence set forth in claim 72 in the conjugate molecule of the claimed population as set forth in claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108.

The specification merely discloses only eight specific immunostimulatory sequences (ISS) selected from the group consisting of SEQ ID NO: 1-8 conjugated to only ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, liens 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

With the exception of the specific population of conjugate comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is insufficient written description about the structure associated with function of all immunostimulatory sequence (ISS). The term "comprises" is open-ended. It expands the ISS nucleotide sequence to include additional nucleotides at either or both ends in addition to nucleotide that is greater than 6 and less than about 200 nucleotides in length. There is inadequate written description about which nucleotides to be added and whether the resulting ISS maintains the same function. Further, the

specification discloses only ISS consisting of 6, 8 and 22 nucleotides in length. The rest of the nucleotides within the ISS comprises the sequence 5'cytosine, guanine-3' is not adequately described.

Given the lack of a written description of *any* additional representative species of ISS comprises the sequence 5'-cytosine, guranine-3' that is greater than 6 and less than about 200 nucleotide in length conjugate to all allergen, all polypeptide, all antigen, pollen allergen, mammal allergen and ISS for the claimed population of conjugate molecules, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/4/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the pending claims are full described in the specification as filed. (2) the burden is on the Examiner to present evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

In response, the scope of the claims encompasses any population of conjugate molecule comprising all antigen or allergen and all polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length. The specification merely discloses only eight specific immunostimulatory sequences (ISS) selected from the group consisting of SEQ ID NO: 1-8 conjugated to only ragweed allergen Amb a1 (See page 72).

With the exception of the specific population of conjugate comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is insufficient written description about the structure associated with function of all immunostimulatory sequence (ISS). The term "comprises" is open-ended. It expands the ISS nucleotide sequence to include additional nucleotides at either or both ends in addition to nucleotide that is greater than 6 and less than about 200 nucleotides in length. There is inadequate written description about which

nucleotides to be added and whether the resulting ISS maintains the same function. Further, the specification discloses only ISS consisting of 6, 8 and 22 nucleotides in length. The rest of the nucleotides within the ISS comprises the sequence 5'cytosine, guanine-3' is not adequately described.

Given the lack of a written description of *any* additional representative species of ISS comprises the sequence 5'-cytosine, guranine-3' that is greater than 6 and less than about 200 nucleotide in length conjugate to all allergen, all polypeptide, all antigen, pollen allergen, mammal allergen and ISS for the claimed population of conjugate molecules, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

8. Claims 75, 83-84 and 86 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "**average** ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen is **at least 1.1**" in Claim 75 represents a departure from the specification and the claims as originally filed. The specification as filed does not provide a clear support for the said phrase.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 71-72, and 83-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "5'purine" in claims 71 has no antecedent basis in base claim 63 because "purine" consists of A or G. However, the amended claim 63 requires that the ISS comprises 5' cytosine (C).

The ISS sequences as set forth in claim 72 have no antecedent basis in base claim 63 because all ISS sequences begin with G or A and not cytosine (C) as required by amended claim 71.

The recitation of "5'purine" in claims 83 has no antecedent basis in base claim 783 because "5'-purine" consists of A or G. However, the amended claim 75 requires that the ISS begins with 5' cytosine (C).

The ISS sequences as set forth in claim 84 have no antecedent basis in base claim 75 because all ISS sequences begin with G or A and not cytosine (C) as required by amended claim 71.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
April 19, 2004

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600